SYNTHESIS, CRYSTALLOGRAPHIC STUDIES AND BIOLOGICAL EVALUATION OF SOME 2-SUBSTITUTED 3-INDAZOLYL-4(3*H*)-QUINAZOLINONES AND 3-INDAZOLYL-4(3*H*)-BENZOTRIAZINONES

Giuseppe Daidone*[a], Salvatore Plescia[a], Demetrio Raffa[a], Domenico Schillaci[a], Benedetta Maggio[a], Franco Benetollo[b], and Gabriella Bombieri[c]

[a]Dipartimento di Chimica e Tecnologie Farmaceutiche, Università di Palermo, Via Archirafi 32, 90123 Palermo, Italy. [b]I.C.T.I.M.A. - C.N.R., Corso Stati Uniti 4, 35127 Padova, Italy. [c]Istituto di Chimica Farmaceutica, Università di Milano, Viale Abruzzi 42, 20131 Milano, Italy

Abstract - A number of new 3-(indazol-3 and 5-yl)-4(3*H*)-quinazolinone and 4(3*H*)-benzotriazinone derivatives were prepared by reaction of 3- or 5-(2-aminobenzamido)indazole with ethyl orthoesters and nitrous acid respectively. Structures were established on the basis of analytical and spectroscopic data. Single-crystal X-ray analysis confirmed the quinazolinone structure of compounds **(5)**. The 4(3*H*)-quinazolinones and 4(3*H*)-benzotriazinones were tested at 200 μg/ml for antimicrobial activity against *C. albicans, C. tropicalis and S. aureus*, at 100 μM for their antitumor effect on human-lymphoblast-like cells and finally at 500 μM for 3α-hydroxysteroid dehydrogenase (3α-HSD) inhibition.

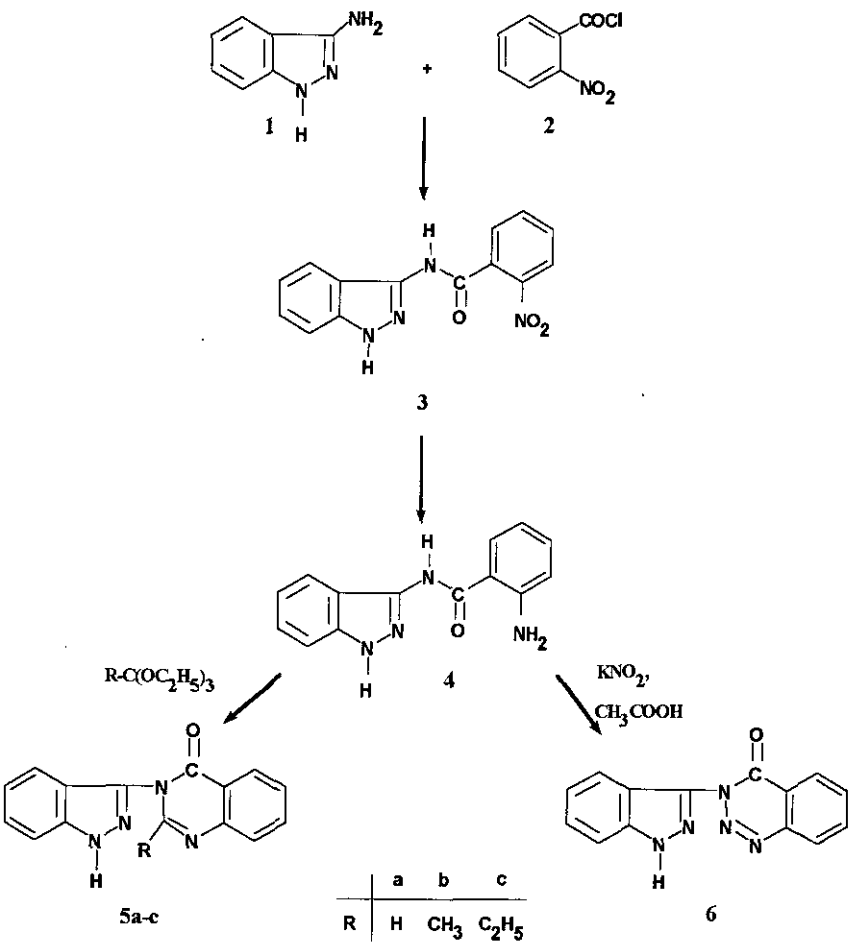
Quinazolin-4(3*H*)-ones and benzotriazin-4(3*H*)-ones bearing a heterocyclic nucleus at the *N*-3 position have attracted an attention as sources for new biologically active agents which are associated with a wide range of pharmaceutical properties such as analgesic, antiinflammatory,

antipyretic,[1,2] antimicrobial,[3] anticonvulsant,[4] antiparkinson,[5] antidepressant, and other central nervous system effects.[6]

Our recent work has provided convenient methods for the preparation of several 3-isoxazolyl and 3-pyrazolyl derivatives, which show antiinflammatory, analgesic, antipyretic, and 3α-HSD inhibition properties.[7-9]

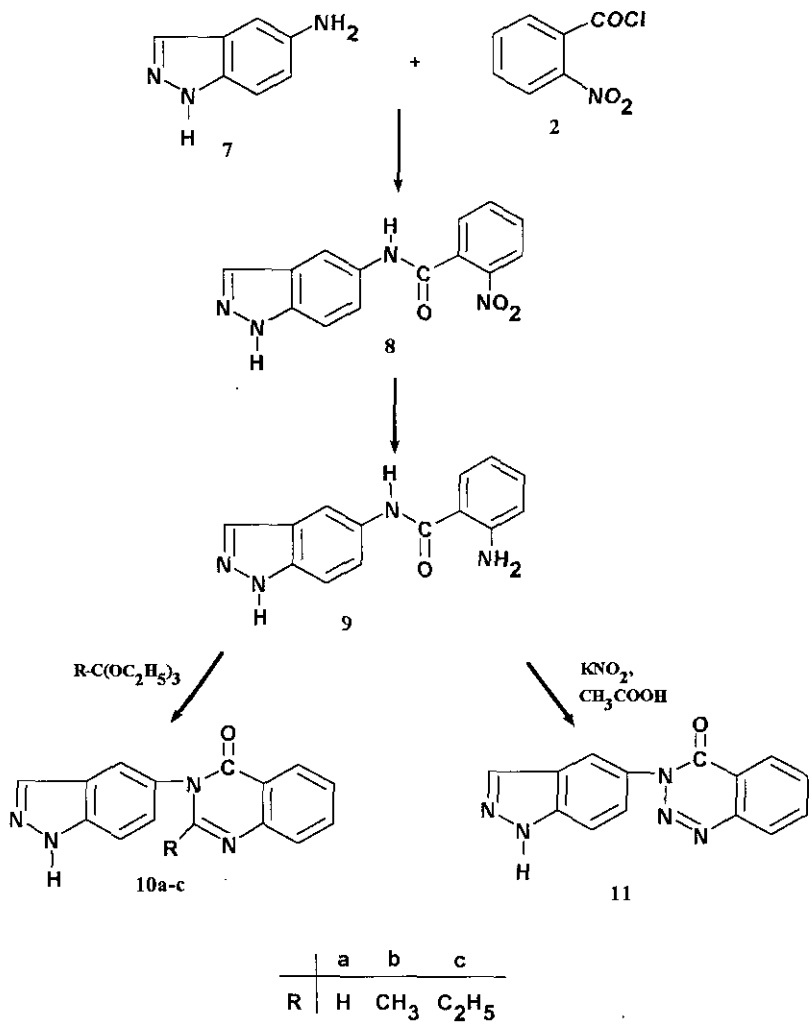
Some indazole derivatives having analgesic and antiinflammatory activities are known, e.g. benzydamine, namely 1-benzyl-3-[3-(dimethylamino)propoxy]-1*H*-indazole, is the active molecule of the antiinflammatory agent Tantum,[10] used for the topical treatment of oropharyngeal and gynecological conditions.

Scheme I



Moreover, a variety of other pharmacological properties, such as antineoplastic[11,12] and antimicrobial activities,[13] have been shown to be associated with certain indazole derivatives. These observations prompted us to incorporate the indazole moiety into the quinazolin-4(3*H*)-one and benzotriazin-4(3*H*)-one nuclei, and to evaluate their possible antiinflammatory activity. With this aim the compounds **(5**, **10)**, and **(6**, **11)** which bear the indazol-3- or -5-yl group at the *N*(3) position of the quinazolinone or benzotriazinone nucleus have been synthesised, in order to clarify the structure-activity relationship for the *N*(3)-heterocycle-substituted derivatives.

Scheme II



	a	b	c
R	H	CH_3	C_2H_5

The syntheses of quinazolinones **(5a-c)** and **(10a-c)** were achieved by treating the appropriate amides **(4)** and **(9)** with orthoesters as shown in the Schemes I and II. When the 5-aminoindazole **(7)** was treated in acetonitrile with equimolar amounts of 2-nitrobenzoyl chloride in the presence of triethylamine, the 5-(2-nitrobenzamido)indazole **(8)** was isolated in 57% yield. Attempts to obtain the 3-(2-nitrobenzamido)indazole **(3)** with the above procedure failed; however, the reaction of 3-aminoindazole **(1)** with 2-nitrobenzoyl chloride **(2)** in pyridine gave the desired compound in 40 % yield.

The indazolic amides **(3)** and **(8)** were transformed by hydrogenation, in presence of palladium on charcoal, to the 2-aminobenzamide derivatives **(4)**, and **(9)** respectively. Condensation of **4** with orthoesters gave 3-(indazol-3-yl)-4(3*H*)-quinazolinones **(5a-c)**. The barrier of internal rotation of the 3-indazol-3-yl group is related to the type of the 2-substituent in series **5**. In fact, the methylene protons of compound **(5c)** are diastereotopic and give rise in the nmr spectrum to two superimposed multiplets, centered at about δ 2.49 and δ 2.40, as a consequence of the slow rotation of the methylene group, on the nmr time scale, due to the encoumbering indazolic moiety at the 3-position of the quinazolinone nucleus.

Condensation of 5-(2-aminobenzamido)indazole **(9)** with orthoesters led to quinazolinones **(10a-c)**. The fragmentation pattern under electron impact of products **(5a-c)** and **(10a-c)**, duplicates that found for the previously described 3-(pyrazol-5-yl)-4(3*H*)-quinazolinones.[14] Lastly, benzotriazinones **(6)** and **(11)** were easily obtained by diazotation of the intermediates **(4)** and **(9)** respectively.

The indazole structure of all compounds is represented as N(H)-1 tautomer, because it has been well established that this form predominates largely in solution. Moreover, in the crystalline state, indazole exists in the N(H)-1 form.[15] Single cristall structure analysis of compound **(5b)** confirmed the above tautomeric form as well as the quinazolinone structure

X-Ray structure of compound (5b)

An ORTEP view of the molecule is shown in Figure 1.

Bond distances are reported in Table 1. They correspond within experimental errors to the literature values.[16] In particular the geometrical features of the indazole moiety are comparable to that of the analogous group in 1-(2,4-dichlorobenzyl)-1*H*-indazole-3-carboxylic acid[17] and in

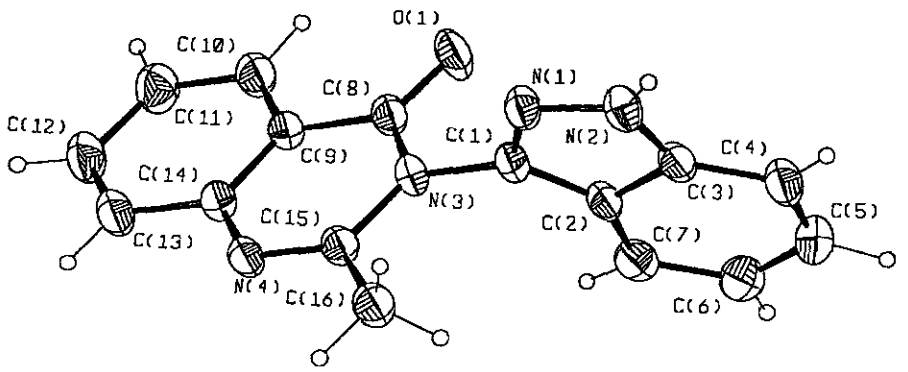


Figure 1 ORTEP drawing of **5b**

benzydamine hydrochloride.[18] The quinazolinone moiety maintains a partial double bond character in the N(4)-C(15) bond distance (1.282(2)Å), while the C(8)-C(9) bond distance adjacent to the C=O group is 1.442(2) Å in line with its single bond character.

Table 1 Bond distances (Å) for compound **(5b)**.

O(1)-C(8)	1.222(2)	N(1)-N(2)	1.355(2)
N(1)-C(1)	1.310(3)	N(2)-C(3)	1.348(3)
N(3)-C(1)	1.428(2)	N(3)-C(8)	1.395(2)
N(3)-C(15)	1.392(2)	N(4)-C(14)	1.391(2)
N(4)-C(15)	1.282(2)	C(1)-C(2)	1.406(3)
C(2)-C(3)	1.397(3)	C(2)-C(7)	1.395(4)
C(3)-C(4)	1.404(3)	C(4)-C(5)	1.353(4)
C(5)-C(6)	1.404(4)	C(6)-C(7)	1.366(3)
C(8)-C(9)	1.442(2)	C(9)-C(10)	1.393(3)
C(9)-C(14)	1.395(3)	C(10)-C(11)	1.374(3)
C(11)-C(12)	1.385(4)	C(12)-C(13)	1.365(3)
C(13)-C(14)	1.395(3)	C(15)-C(16)	1.488(3)

The molecular structure is characterized by two planar moieties, the two fused systems, quinazolinone and indazole, connected by C(1)-N(3) with a torsion angle C(15)-N(3)-C(1)-N(1) of -80.4(2)° (gauche conformer). The crystal packing shows a net-work of hydrogen bond interactions involving the crystallized water molecules (one per asymmetric unit) and the proton

of the indazole group. The water oxygen acts either as acceptor (N(2) proton) or donor of protons to N(4) and to the carbonyl oxygen (Table 2).

Table 2 Hydrogen bond interactions for **5b**.

	Donor Acceptor	dist.(Å)	H···A (Å)	Angle (°)
N(2)-H(2)	N(2).....O(2)^{i}	2.737(3)	1.81(3)	164(2)
O(2)-H(20)	O(2).....N(4)^{ii}	2.938(3)	2.12(3)	152(3)
O(2)-H(21)	O(2).....O(1)^{iii}	2.805(2)	1.97(4)	171(3)

(^{i} at x,-1+y,-1+z; ^{ii} at 1-x,1-y,1-z; ^{iii} at -x,1-y,1-z)

Additional π like interactions are present between the indazole moieties centrosymmetrically related, and the significant contacts are C(3)···N(2)^{iv} 3.475(3), C(4)···N(1)^{iv} 3.621(3), C(4)···N(2)^{iv} 3.562(3)Å (^{iv} at -x,-y,-z), (Figure 2).

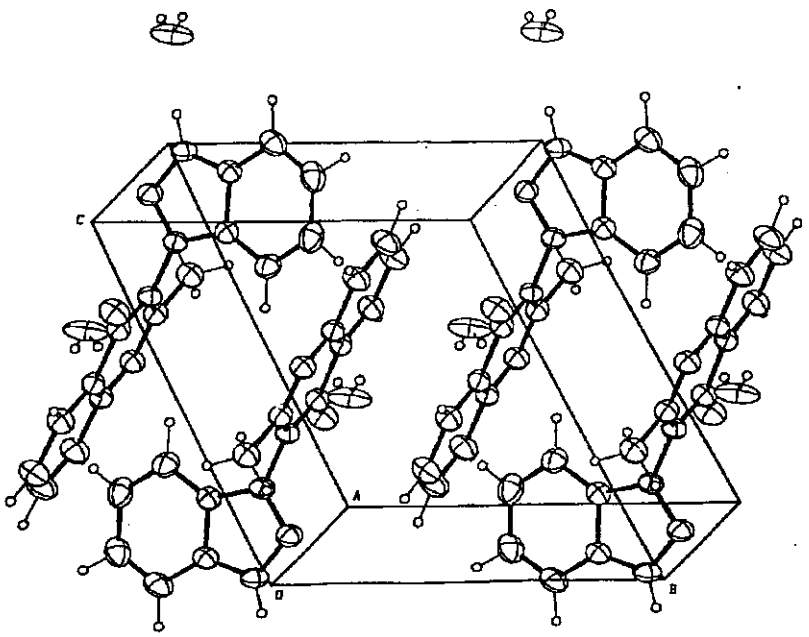


Figure 2 Crystal packing of **5b**

Biological Results

In vitro inhibition of the 3α-hydroxysteroid dehydrogenase is indicative of antiinflammatory activity *in vivo*.[19,20] Inhibition activity on 3α-hydroxysteroid dehydrogenase of compounds **(5a-c)**, **(6)** and **(10a-c)**, having spectroscopic and solubility requisites for test execution, was measured at 0.5 mM but no enzyme inhibition appeared. The compounds **(5a-c)**, **(10a-c)**, **(6),** and **(11)** were tested for antitumor and antimicrobial activities which have been suggested for some indazole derivatives.[11-13] For antimicrobial activity, the compounds were tested against *S. aureus* as well as against two fungi (*C. albicans* and *C. tropicalis*) but at the tested concentration (200 μg/ml) they did not result active. The antineoplastic activity was tested at 100 μM against human lymphoblastic-like cells from a *Burkitt lymphoma* (Raji cells) and the compound **(5a)** showed a 57.3% cell growth inhibition.

EXPERIMENTAL

All melting points were taken from a Büchi 530 capillary melting point apparatus and are uncorrected. Infrared spectra were determined in nujol mull with a Jasco IR-810 spectrophotometer, and nmr spectra (DMSO-d_6, unless otherwise specified) were recorded on a Brüker AC-E 250 MHz spectrometer using tetramethylsilane as internal standard. Mass spectrometric measurements were performed on a VG ZAB 2F instrument operating in electron impact (EI) conditions (70eV, 200μA). Microanalyses were performed in the laboratories of the Institut de Chimie Pharmaceutique, Université de Genève, Switzerland.

3-(2-Nitrobenzamido)indazole (3). To a magnetically stirred cold solution (ice bath 0-5 °C) of 3-aminoindazole **(1)** (1.1 g, 8 mmol) in pyridine (10 ml, 0.12 mol), 2-nitrobenzoyl chloride (1.48 g, 8 mmol) was added dropwise. The reaction mixture was left under magnetic stirrer overnigth then poured in crushed ice. The mixture thus obtained was extracted with ethyl acetate (3X100 ml). The organic phases, first washed with 0.1 M aqueous hydrochloric acid (100 ml) then with water (100 ml), were dried (sodium sulfate) and evaporated *in vacuo*. The gum residue was boiled in ether (50 ml) for 5 min, the solid product which separated was filtered off and crystallized from ethanol; yield 0.9 g (40 %); mp 196-197 °C; ir (nujol) (cm^{-1}) 3330-3100, 1660; ^{1}H-nmr (δ) 7.12-8.18 (8H, a set of signals, $2XC_6H_4$), 11.15 (1H, s, exchangeable with D_2O, NH), 12.84 (1H, s, exchangeable with D_2O, NH); *Anal.* Calcd for $C_{14}H_{10}N_4O_3$: C, 59.57; H, 3.57; N, 19.85. Found: C, 59.70; H, 3.55; N, 19.67.

3-(2-Aminobenzamido)indazole (4). To a solution of **3** (1 g, 3.5 mmol) in ethanol (250 ml), a small amount of palladium on charcoal as catalyst was added. The mixture was left under hydrogenation for 24 h in a Parr apparatus, at 40-45 psi, then was filtered and evaporated under reduced pressure. The crude residue was crystallized from ethanol; yield 0.4 g (45%); mp 214-216 °C; ir (Nujol) (cm^{-1}) 3500-3020, 1670; ^{1}H-nmr (δ) 6.54-7.85 (10H, a set of signals, $2XC_6H_4$ and NH_2 exchangeable with D_2O),10.50 (1H, s, exchangeable with D_2O, NH), 12.77 (1H, s, exchangeable with D_2O, NH); *Anal.* Calcd for $C_{14}H_{12}N_4O$: C, 66.65; H, 4.79; N, 22.21. Found: C, 66.37; H, 4.93; N, 21.90.

General procedure for 3-(indazol-3-yl)quinazolin-4-(3*H*)-ones (5a-c). The indazolyl-2-aminobenzamide **(4)** (1 g, 4 mmol) was dissolved by heating in the opportune amount of triethyl orthoesters (25 mmol) and the solution was refluxed gently for 5 h. After this time the solution was cooled to room temperature. The precipitate was filtered and recrystallized from ethanol; yield 43-55 %. **5a**: mp 202-204 °C; ms (m/z) 262 (M^+); ir (nujol) (cm^{-1}) 3200-3000, 1710; ^{1}H-nmr (δ) 6.95-9.00 (9H, a set of signals, $2XC_6H_4$ and quinazolinone H-2), 13.52 (1H, s, exchangeable with D_2O, NH); *Anal.* Calcd for $C_{15}H_{10}N_4O$: C, 68.69; H, 3.84; N, 21.36. Found: C, 68.50; H, 3.97; N, 21.10. **5b**: mp 149-150 °C; ms (m/z) 276 (M^+); ir (nujol) (cm^{-1}) 3200-3000, 1710-1690; ^{1}H-nmr (δ) 2.15 (3H, s, CH_3), 7.16-8.17 (8H, a set of signals, $2XC_6H_4$), 13.54 (1H, s, exchangeable with D_2O, NH); *Anal.* Calcd for $C_{16}H_{12}N_4O\cdot H_2O$: C, 65.29; H, 4.79; N, 19.03. Found: C, 65.21; H, 4.85; N, 18.91. **5c**: mp130-132 °C; ms (m/z) 290 (M^+); ir (nujol) (cm^{-1}) 3560-3040, 1680; ^{1}H-nmr (δ) 1.10 (3H, t, CH_3, J=7.4 Hz), 2.29-2.51 (2H, superimposed multiplets, CH_2), 7.16-8.16 (8H, a set of signals, $2XC_6H_4$), 13.54 (1H, s, exchangeable with D_2O, NH); *Anal.* Calcd for $C_{17}H_{14}N_4O\cdot H_2O$: C, 66.22; H, 5.23; N, 18.17. Found: C, 66.14; H, 5.28; N, 17.85.

3-(Indazol-3-yl)-1,2,3-benzotriazin-4(3*H*)-one (6). To a magnetically stirred cold (ice bath, 0-5 °C) solution of compound **(4)** (1.8 g, 7.1 mmol) in acetic acid (120 ml), potassium nitrite (1.2 g, 14.1 mmol) was added dropwise. Stirring was continued for 1 h at 0-5 °C and then the solution was warmed to room temperature. The white precipitate obtained by addition of cold water (200 ml) to the solution was filtered off, washed with water then crystallized from ethanol; yield 1.49 g (81 %); mp 210-212 °C; ms (m/z): 235 (M^+-N_2); ir (nujol) (cm^{-1}) 3380-3120, 1710; ^{1}H-nmr

($CDCl_3$) (δ) 7.19-8.54 (8H, a set of signals, $2XC_6H_4$), 11.05 (1H, br s, exchangeable with D_2O, NH); *Anal.* Calcd for $C_{14}H_9N_5O$: C, 63.87; H, 3.45; N, 26.20. Found: C, 63.67; H, 3.75; N, 26.10.

5-(2-Nitrobenzamido)indazole (8). A mixture of 2-nitrobenzoyl chloride **(2)** (9.3 g, 50 mmol) and 5-aminoindazole **(7)** (7 g, 50 mmol) was dissolved in acetonitrile (250 ml). After 3 h of reflux, three portions of triethylamine (2.5 ml each, 17.8 mmol) were added at 1 h intervals and reflux was continued for 1 h after the last addition. The solution was evaporated *in vacuo*, the residue was treated with few ml of ether until it became solid, filtered off and crystallized from ethanol; yield 8.1 g (57 %); mp 264 °C; ir (nujol) (cm^{-1}) 3300-3060, 1660; ^{1}H-nmr (δ) 7.52-8.20 (8H, a set of signals, C_6H_4, C_6H_3 and indazole H-3), 10.67 (1H, s, exchangeable with D_2O, NH), 13.06 (1H, s, exchangeable with D_2O, NH); *Anal.* Calcd for $C_{14}H_{10}N_4O_3$: C, 59.57; H, 3.57; N, 19.85. Found: C, 59.49; H, 3.60; N, 19.61.

5-(2-Aminobenzamido)indazole (9). Compound **(9)** was obtained as described for compound **(4)** starting from amide **(8)** (1 g, 3.5 mmol) in ethanol (200 ml); yield 0.6 g (69 %); mp 240 °C (ethanol); ir (nujol) (cm^{-1}) 3460-3050, 1635; ^{1}H-nmr (δ) 6.31 (2H, s, exchangeable with D_2O, NH_2), 6.56-8.15 (8H, a set of signals, C_6H_3, C_6H_4 and indazole H-3), 10.00 (1H, s, exchangeable with D_2O, NH), 12.98 (1H, s, exchangeable with D_2O, NH); *Anal.* Calcd for $C_{14}H_{12}N_4O$: C, 66.65; H, 4.79; N, 22.21. Found: C, 66.43; H, 4.83; N, 21.91.

General procedure for 3-(indazol-5-yl)quinazolin-4-(3*H*)-ones (10a-c).

They were obtained, as **5a-c**, starting from amino derivative **(10)** (1 g, 4 mmol) and the appropiate triethyl orthoester (25 mmol); yield 85-90 %. **10a**: mp 264 °C (ethanol); ms (m/z) 262 (M^+); ir (nujol) (cm^{-1}) 3300-3020, 1680; ^{1}H-nmr (δ) 7.46-8.40 (9H, a set of signals, C_6H_3,C_6H_4, indazole H-3 and quinazolinone H-2), 13.35 (1H, s, exchangeable with D_2O, NH); *Anal.* Calcd for $C_{15}H_{10}N_4O$: C, 68.69; H, 3.84; N, 21.36. Found: C, 68.63; H, 3.94; N, 21.17. **10b**: mp 294-296 °C (ethanol); ms (m/z) 276 (M^+); ir (nujol) (cm^{-1}) 3290-3090, 1655; ^{1}H-nmr (δ) 2.15 (3H, s, CH_3), 7.36-8.19 (8H, a set of signals, C_6H_3, C_6H_4 and indazole H-3), 13.37 (1H, s, exchangeable with D_2O, NH); *Anal.* Calcd for $C_{16}H_{12}N_4O$: C, 69.55; H, 4.37; N, 20.27. Found: C, 69.18; H, 4.58; N, 19.91. **10c**:mp 225-227 °C (ethanol); ms (m/z) 290 (M^+); ir (nujol) (cm^{-1}) 3400-3100, 1660; ^{1}H-nmr (δ) 1.13 (3H, t, CH_3, J=7.5 Hz), 2.38 (2H, m, CH_2), 7.35-8.19 (8H, a set of signals, C_6H_3, C_6H_4 and indazole H-3), 13.36 (1H, s, exchangeable with D_2O, NH); *Anal.* Calcd for $C_{17}H_{14}N_4O$: C, 70.33; H, 4.86; N, 19.30. Found: C, 70.13; H, 4.94; N, 18.99.

3-(Indazol-5-yl)-1,2,3-benzotriazin-4(3*H*)-one (11). Compound **(11)** was obtained as described for compound **(6)** starting from amide **(9)**; yield 80 %; mp 293-295 °C (ethanol); ms (m/z) 235 (M^+-N_2); ir(nujol) (cm^{-1}) 3360-3100, 1670; ^{1}H-nmr (δ) 7.60-8.34 (8H, a set of signals, C_6H_3, C_6H_4 and indazole H-3), 13.41 (1H, s, exchangeable with D_2O, NH); *Anal.* Calcd for $C_{14}H_9N_5O$: C, 63.87; H, 3.54; N, 26.60. Found: C, 63.67; H, 3.59; N, 26.30.

Crystallographic measurements

Crystal data for **5b**, $C_{16}H_{12}N_4O\cdot H_2O$, M=294.31, yellow prism (0.40 x 0.38 x 0.60 mm) triclinic, space group $P\bar{1}$, *a*=9.033(3), *b*=9.212(3), *c*=9.661(2)Å, α=116.04(3), β=90.63(3), γ=93.14(2)°; V = 720.7(4)Å^3 , Z = 2, Dx = 1.356 Mg m^{-3}, λ = (MoKα) = 0.71069Å , μ(Mokα) = 0.93 cm^{-1}, F(000) = 308, T = 293 K. X-Ray diffraction data were recorded on a four-circle Philips PW1100 (Febo System) diffractometer operating in θ/2θ scan mode with graphite-monochromated (Mo-Kα) radiation λ=0.71069 Å), following standard procedures. 3009 Reflections were measured ($2\theta_{max}$ = 52°). There were no significant fluctuations of intensities other than those expected from Poisson statistics.The intensity data were corrected for Lorentz-Polarization effects and for absorption, as described by North *et al.*[21] The structure was solved by direct methods.[22] Refinement was carried out by full-matrix least-squares; the function minimized was $\Sigma w(Fo^2-Fc^2)^2$, with weighting scheme $w=1/[\sigma^2(Fo^2)+(0.0510P)^2+0.28P]$, where $P=max(Fo^2+2Fc^2)/3$. All non-hydrogen atoms were refined with anisotropic thermal parameters. The H-atoms were located from difference Fourier maps and refined isotropically. For a total of 255 parameters, $wR'=[\Sigma w(Fo^2-Fc^2)^2/\Sigma w(Fo^2)^2]^{1/2}$ =0.126 (on F^2) , S=1.140, and conventional R=0.047, based on F values of 2374 reflections having $Fo^2 \geq 3\sigma(Fo^2)$. Structure refinement and final geometrical calculations were carried out with SHELXL-93 programs,[23] drawings were produced using *ORTEP II*. [24]

• *Additional material available from the Cambridge Crystallographic Data Center comprises the fractional atomic coordinates and anisotropic thermal parameters .*

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